REMARKS

Claims 44 to 65 were pending in this application. Claims 58 to 61 have been canceled, without prejudice, and new claims 66 to 68 have been added. Applicants reserve the right to pursue the subject matter of the canceled claims in the present application or a related application(s). Claims 44 to 48 have been amended to incorporate the limitations of canceled claim 60. Support for the amendments to claims 44 to 48 can be found in the specification at, *e.g.*, pages 25 to 26, ¶¶ 84 and 85; and Figure 1. Support for new clam 66 can be found in the specification at, *e.g.*, page 153, ¶ 435. Support for new claims 67 and 68 can be found in the specification at, *e.g.*, page 70, ¶ 173 and page 73, ¶ 181 and page 79, ¶ 204 to page 81, ¶ 207. Thus, no new matter has been added. After entry of the present Amendment, claims 44 to 57 and 62 to 68 will be pending.

Applicants note that the Detailed Action section of the Office Action, mailed January 13, 2010, states that the Office Action is "made NON-FINAL to address the new grounds of rejection." See January 13, 2010 Office Action at page 2. However, the Office Action Summary indicates that the January 13, 2010 Office Action is final. Examiner Mummert in a teleconference on July 6, 2010 confirmed that the January 13, 2010 Office Action is non-final. Accordingly, Applicants have replied to the January 13, 2010 Office Action on the basis that it is non-final.

In the event that the U.S. Patent and Trademark Office determines that the January 13, 2010 Office Action is final, Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated January 13, 2010 of the Primary Examiner finally rejecting claims 44 to 65 of the application, and authorize the payment of the required fee (estimated to be $270) to Jones Day Deposit Account No. 50-3013.

The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

1. The Rejection over Hyder in view of Vagner

Claims 44, 46, 47, 49-54, 60, and 61 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hyder *et al.*, 2000, Cancer Research, 60: 3183-3190 ("Hyder") in view of Vagner *et al.*, 2001, EMBO Reports, 2(10): 893-898 ("Vagner"). Applicants submit that claims 60 and 61 have been canceled, rendering the rejection of these

claims moot. Applicants respectfully disagree with the rejection of claims 44, 46, 47, and 49-54 for the reasons detailed below.

In the consideration and determination of obviousness under 35 U.S.C. § 103(a), the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 10 (1966) stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

When an invention combines two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. *KSR Intern. Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1737 (2007). If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. *Id.* at 1737. A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. *Id.* at 1737.

Further, the relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

Applicants respectfully submit that independent claims 44, 46, and 47 are patentable over Hyder because Hyder does not teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, comprising contacting a compound with a human cell engineered to express a reporter protein encoded by a reporter mRNA operably linked to the full-length 5' untranslated ("UTR") and the full-length 3' UTR of the human VEGF mRNA, as required by claims 44, 46, and 47.

The focus of Hyder is to understand the molecular mechanism(s) underlying the induction of VEGF transcription in response to estrogen. In the investigation of such molecular mechanisms, Hyder identified eleven (11) short DNA sequences within the rat VEGF genomic sequence that have homology to a consensus estrogen response element, which has been shown to induce DNA transcription in response to estrogens (see Figure 1 of Hyder). Hyder demonstrates that two of the short DNA sequences, which were found in the

5' and 3' untranslated regions of the rat VEGF genomic sequence, specifically bind to human estrogen receptors in gel shift assays (see, *e.g.*, Hyder at Figures 2 and 3, and page 3185, col. 1, 2nd full para to page 3185, col. 2, 1st full para). The fact that the two short DNA sequences with homology to a consensus estrogen response element were found in the 5' and 3' untranslated regions of rat VEGF would not have suggested to one of ordinary skill in the art that the mRNA transcribed from such DNA sequences would have any affect on mRNA translation. Rather, given the homology of such DNA sequences to a consensus estrogen response element, the specific binding of two of those DNA sequences to human estrogen receptors, and the known role of estrogen response elements in the induction of DNA transcription in response to estrogen, one of ordinary skill in the art would not have been motivated to use the described short DNA sequences for anything other than inducing rat VEGF transcription in the presence of estrogen.

In order to assess the transcriptional activities of the short DNA sequences with homology to a consensus estrogen response element, Hyder produced reporter constructs in which tandem copies of either the short DNA sequence within the 5' UTR of rat VEGF DNA or the 3'UTR of rat VEGF DNA, in either the endogenous or reverse orientation, were ligated upstream of a thymidine kinase promoter linked to a luciferase reporter. Hyder transfected such reporter constructs into HeLa cells along with plasmids encoding an estrogen receptor subtype and then the cells were incubated with or without estrogen (see Hyder at page 3185, col. 2, last para. to page 3187, col. 2, first para. and Figure 5). Luciferase activity was determined 24 hours after the incubation with or without estrogen (see Hyder at page 3187, Figure legend for Figure 5; Figure 5). Because of the role of estrogen receptor in the induction of DNA transcription in response to estrogen, none of the reporter assays described in Hyder were performed without co-transfecting a plasmid encoding an estrogen receptor subtype into cells. In contrast, the claimed invention which recites methods for identifying a compound that modulates mRNA translation governed by the untranslated regions of the human VEGF mRNA does not require co-transfection of a plasmid encoding an estrogen receptor subtype. Moreover, the reporter assays that are described in Hyder do *not* comprise a reporter protein encoded by a reporter mRNA operably linked to both the full-length 5' UTR and full-length 3' UTR of the human VEGF mRNA, as required by the claims. On the contrary, the reporter constructs that were used in the reporter assays of Hyder contain tandem copies of the DNA sequences found in the 5' or 3' UTR of genomic rat VEGF which

have homology to a consensus estrogen response element (cERE). The legend of Figure 1 in Hyder states "B, sequences of the VEGF regions (sense strand) homologous to the cERE." (Hyder at Figure 1 legend at page 3184). In addition, the description of Figure 1 in the results section states that ".. . 11 sequences with a minimum 60% homology to the cERE .. . and [t]hese sequences are shown in Fig. 1B, and their location in the VEGF gene is indicated in Fig. 1A." (Hyder at page 3185, 1st col., 1st full para.). Thus, the Examiner's contention at page 6 of the Office Action that Hyder discloses the full-length 5' and 3' UTRs of human VEGF mRNA is in error.

There is no teaching or suggestion in Hyder to perform a screening assay to identify compounds that modulate human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, by performing reporter assays using reporter constructs that encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, much less a screening assay, such as recited in claim 46, which also requires a reporter construct comprising the 5' and 3' UTRs of a mRNA other than VEGF. Moreover, Hyder does not provide any reason that would have prompted a person of ordinary skill in the art to perform a screening assay to identify compounds that modulate human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, by performing such a reporter assay(s). Further, given the known role of estrogen response elements for inducing DNA transcription in response to estrogen, one of ordinary skill in the art would not have had a reasonable expectation of successfully identifying a compound that modulates human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA using reporter constructs comprising the DNA estrogen-responsive sequences identified by Hyder.

Vagner does not cure the deficiencies of Hyder. Vagner is a review article that discusses cap-independent translation via internal ribosome entry sites (IRES). The primary teaching of Vagner is that cap-independent translation requires a particular mRNA structure needed to initiate ribosomal interaction with an IRES element in the mRNA 5' UTR. Nowhere does Vagner teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, comprising contacting a compound with a human cell engineered to express a reporter protein encoded by a reporter mRNA operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, as required by claims 44, 46, and 47.

The Examiner points to Figure 1 and the legend of Figure 1 in Vagner for asserting that the 3' UTR and 5' UTR of mRNA interact through "standard translation" machinery and that this interaction is disrupted or is unnecessary during IRES mediated translation (see Office Action at page 7, 1st para.). Applicants are unable to locate this teaching anywhere in Vagner, let alone in Figure 1 or the figure legend of Figure 1 of Vagner. A reading of Vagner will clearly show that the term "standard translation" has not been used in Vagner. Moreover, Applicants respectfully submit that the Examiner is scientifically incorrect in arguing that Vagner ostensibly stands for the principle that cap-independent "standard translation" is different from cap-independent translation. The Examiner appears to have derived this term *sua sponte* and inappropriately imputed the term to Vagner.

Furthermore, the Examiner states that "one of ordinary skill in the art at the time the invention was made [would,] ... [a]s taught by Vagner, 'have adjusted the teachings of Hyder to recognize that the compound disrupts the interaction between the 3'UTR and 5'UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation of success' (Figure 1 legend, p. 894)" (see the Office Action at page 7, 2nd para.). Applicants respectfully submit that Applicants are unable to locate the foregoing teaching/quotation anywhere in Vagner. Applicants respectfully point out that the only teaching in Vagner with respect to VEGF is that cap-independent translation of VEGF is induced by hypoxia (see Vagner at page 895, col. 2, 3rd para.). Accordingly, Applicants respectfully contend that, contrary to the Examiner's allegations, there is no hint or suggestion anywhere in Vagner that cap-independent translation disrupts an interaction between the 5' UTR and the 3' UTR of any mRNA, let alone human VEGF mRNA.

As a result, the argued combination of the teachings of Hyder and Vagner made by the Examiner does not make scientific sense. As discussed above, Hyder relates to regulation of DNA transcription. The teaching of Vagner relates to cap-dependent and cap-independent regulation of mRNA translation. One of ordinary skill in the art would not correlate the mechanism of estrogen receptor subtypes interacting with estrogen receptor element DNA sequences for inducing transcription of VEGF DNA with cap-dependent or cap-independent translation of VEGF mRNA because the mechanism according to Hyder produces pre-mRNA and the one according to Vagner produces protein. Thus, given the unrelatedness of the teachings of Hyder and Vagner, there is no reason that would have prompted a person of

ordinary skill in the relevant field to combine the teachings of Hyder and Vagner, let alone combine them and arrive at the claimed invention with a reasonable expectation of success.

In view of the foregoing, Applicants submit that Hyder in view of Vagner, fails to render obvious claims 44, 46, 47, 49-54, 56, 60, and 61, and respectfully request that this rejection be withdrawn.

2. The Rejection over Hyder in view of Vagner and Levy.

Claims 45, 49-54, 56, and 60 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hyder in view of Vagner and further in view of Levy *et al.*, 1998, J. Biol. Chem. 273(11): 6417-6423 ("Levy"). Applicants submit that claim 60 has been canceled, rendering the rejection of this claim moot. Applicants respectfully disagree with the rejection of claims 45, 49-54, and 56 for the reasons detailed below.

Independent claim 45 is patentable over Hyder and Vagner because, as discussed above, neither Hyder nor Vagner teach or suggest, or provide any reason that would have prompted a person of ordinary skill in the art to perform a screening assay for identifying compounds that modulate human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA using reporter constructs that encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, as required by claim 45. Furthermore, Applicants submit that Hyder and Vagner do not teach or suggest performing reporter assays that comprise a cell-free translation mixture expressing a reporter protein encoded by a reporter mRNA, as required by claim 45. Moreover, contrary to the Examiner's contentions, there is no hint or suggestion in Vagner of a disruption in an interaction between the 5' UTR and the 3' UTR of any mRNA, let alone human VEGF mRNA.

Levy does not cure the deficiencies of either Hyder or Vagner. Levy is a study aimed at determining whether a novel 36-kDa RNA binding protein, HuR, is involved in hypoxic stabilization of VEGF. Levy describes *in vitro* binding experiments that show that the HuR protein binds with high affinity and specificity to a 45 nucleotide fragment within the 3'UTR of VEGF to regulate VEGF mRNA stability under hypoxic conditions (see Levy, page 6419, col. 1 to col. 2). Levy also describes actinomycin D chase experiments that showed that antisense-mediated inhibition of HuR expression blocked hypoxic stabilization of VEGF mRNA (see Levy at page 6419, 2nd col., last para. to page 6420, 2nd col., 2nd para.) and that overexpression of HuR increased VEGF mRNA stability (see Levy at page 6420, col. 2, 3rd

para. to page 6421, col. 2, 1st para.). Levy further describes an *in vitro* RNA degradation assay using capped, polyadenylated VEGF 3' UTR transcripts and S-100 cytoplasmic extracts to show that the addition of exogenous HuR stabilized VEGF mRNA significantly (see Levy at page 6421, col. 2, 2nd para.). Levy compares VEGF mRNA stabilization by the HuR protein under normoxic and hypoxic conditions, but nowhere does Levy teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with a cell-free translation mixture expressing a reporter protein encoded by a reporter mRNA operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, as required by claim 45. There is no hint or suggestion in Levy of any type of reporter assay, let alone one that involves cells or cell-extracts containing the reporter constructs used in the claimed methods. As such, Levy does not cure the deficiencies of either Hyder or Vagner.

Moreover, even if the teachings of Hyder, Vagner, and Levy were combined, the combined teachings would not result in the screening assays of the claimed invention. The combined teachings of Hyder, Vagner, and Levy would, at most, suggest further assessing the role of the estrogen response elements identified by Hyder using assays similar to those described in Levy.

In view of the foregoing, Applicants submit that Hyder in view of Vagner and Levy, fails to render obvious claims 45, 49-54, 56, and 60, and respectfully request that this rejection be withdrawn.

3. The Rejection over Hyder in view of Vagner and Stein

Claims 46 and 47 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hyder in view of Vagner and further in view of Stein *et al.*, 1998, Mol. Cell. Biol. 18(6): 3112-63119 ("Stein"). Applicants respectfully disagree with the rejection for the reasons detailed below.

As discussed above, independent claims 46 and 47 are patentable over Hyder and Vagner because, as discussed above, neither Hyder nor Vagner teach or suggest, or provide any reason that would have prompted a person of ordinary skill in the art to perform a screening assay for identifying compounds that modulate human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, by performing reporter

assays using reporter constructs that encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA. Moreover, there is no teaching or suggesting in Hyder or Vagner of contacting a screened compound with a second human cell (as in claim 46) or human cells contained in a plurality of wells (as in claim 47), wherein the cells are engineered to express a reporter protein encoded by a reporter mRNA operably linked to a 5'UTR and a 3'UTR of a different mRNA, and wherein the 5' UTR and the 3' UTR of the different mRNA are not the 5' UTR and the 3' UTR of the human VEGF mRNA, in order to identify a compound that modulates human VEGF mRNA translation governed by the untranslated regions of human VEGF mRNA, as required by claims 46 and 47. Also, as discussed above, contrary to the Examiner's contentions, there is no hint or suggestion in Vagner of a disruption in an interaction between the 5' UTR and the 3' UTR of any mRNA, let alone human VEGF mRNA.

Stein does not cure the deficiencies of either Hyder or Vagner. The Examiner states that "[w]ith regard to claims 46-47, Stein teaches (b) contacting a compound with a panel of cells, wherein each human cell in the panel is isolated from each other and each human cell is engineered to express a reporter protein encoded by a reporter mRNA operably linked to a 5'UTR and a 3'UTR of a mRNA other than the human VEGF mRNA (p. 3115, Figure 3, where the reporter was operably linked to UTR of BiP mRNA instead of VEGF)" (see the Office Action at page 14, last para. to page 15, first para.). Applicants respectfully submit that the Examiner has erroneously characterized the teaching of Stein. Stein describes reporter assays performed under normoxic and hypoxic conditions using monocistronic and bicistronic reporter gene constructs in order to confirm that the murine 5'UTR of VEGF contains a functional IRES (see Stein at page 3114, col. 2, last para. to page 3115, col. 1, 1st para.). Stein also teaches reporter assays performed under normoxic and hypoxic conditions using monocistronic and bicistronic reporter gene constructs in order to compare the relative strength of the IRES in the 5'UTR of murine VEGF to the IRES in BiP (see Stein at page 3115, col. 1, last para. to col. 2, 1st para.). The monocistronic and bicistronic reporter constructs of Stein contain either: (i) the 5'UTR of murine VEGF linked to SeAP, (ii) a mutant of the 5'UTR of murine VEGF linked to SeAP, or (iii) the 5' UTR of BiP linked to SeAP. None of the constructs described in Stein contain both the full-length 5'UTR and full-length 3'UTR of human VEGF (see Stein at page 3114, col. 2, last para. to page 3115, col. 2, 1st para. and page 3113, Fig. 1 description). Furthermore, the cells used to perform the

reporter assays in Stein were never contacted with a compound, but rather were exposed to normoxic or hypoxic conditions, wherein hypoxic conditions are characterized by a reduction in oxygen available to the cells, under which IRES-induced reporter expression was determined. Thus, Stein would not have taught or suggested to a person of ordinary skill in the art a method for identifying a compound that modulates human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, comprising contacting a compound with a human cell engineered to express a reporter protein encoded by a reporter mRNA operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, as required by claims 46 and 47. Moreover, nowhere does Stein teach or suggest contacting the compound with human cells in a plurality of wells, wherein each well contains human cells engineered to express a reporter protein encoded by a reporter mRNA operably linked to the 5' UTR and 3' UTR of a different mRNA, and wherein the 5' UTR and the 3' UTR of the different mRNA are not the 5' UTR and the 3' UTR of the human VEGF mRNA, as required in claim 47. As such, Stein does not cure the deficiencies of either Hyder or Vagner.

Further, even if the teachings of Hyder, Vagner, and Stein were combined, the combined teachings would not result in the screening assays of the claimed invention. The combined teachings of Hyder, Vagner, and Stein would, at most, suggest assessing whether the estrogen response elements identified by Hyder contain IRES elements in the 5' UTR alone or provide IRES induced activity under normoxic or hypoxic conditions using assays described in Stein, or assessing the effect of the estrogen response elements on inducing IRES activity under normoxic and hypoxic conditions.

In view of the foregoing, Applicants submit that Hyder in view of Vagner and Stein fails to render obvious claims 46 and 47, and respectfully request that this rejection be withdrawn.

4. The Rejection over Hyder in view of Vagner, Levy and Stein

Claim 48 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hyder in view of Vagner and Levy and further in view of Stein. Applicants respectfully disagree with the rejection for the reasons detailed below.

As discussed above, independent claim 48 is patentable over Hyder, Vagner and Levy because, as discussed above, neither Hyder, Vagner nor Levy teach or suggest, or provide any

reason that would have prompted a person of ordinary skill in the art to perform a screening assay for identifying compounds that modulate human VEGF mRNA translation governed by the untranslated regions of human VEGF mRNA, by performing reporter assays using reporter constructs that encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA. Moreover, there is no teaching or suggestion in Hyder, Vagner or Levy of contacting a screened compound with either a cell-free translation mixture or a cell-free translation mixture expressing a reporter protein encoded by a reporter mRNA operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, let alone a method for identifying a compound that modulates human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA using a cell-free translation mixture expressing a first reporter protein encoded by a first reporter mRNA operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA and a cell-free translation mixture expressing a second reporter protein encoded by a second reporter mRNA operably linked to a 5'UTR and a 3'UTR of a different mRNA, wherein the 5' UTR and the 3' UTR of the different mRNA are not the 5' UTR and the 3' UTR of the human VEGF mRNA, as required by claim 48.

As discussed above, Stein does not cure the deficiencies of either Hyder, Vagner or Levy. Applicants respectfully submit that the teaching of Stein does not scientifically support the Examiner's argument that "one of ordinary skill in the art...would have motivated to have adjusted the teachings of Hyder, Vagner and Levy to include...an additional control, including the 5' and 3' UTR regulatory regions from a different gene as taught by Stein." (see the Office Action at page 18, end of first partial paragraph). Stein describes *cell-based* reporter assays to determine whether VEGF mRNA has an IRES which provides IRES-induced translation, and the relative strength of the IRES in either the VEGF or BiP mRNA. To make such determinations, Stein uses bicistronic reporter gene constructs containing either: (i) the 5'UTR of murine VEGF linked to SeAP, (ii) a mutant of the 5'UTR of murine VEGF linked to SeAP, or (iii) the 5' UTR of BiP linked to SeAP. One of ordinary skill in the art would have recognized that such bicistronic reporter gene constructs are used in cell-based assays to specifically test a mRNA sequence for the presence of an IRES or whether the mRNA has IRES-inducible activity. Thus, the Examiner's allegation of the obviousness of claim 48 would not have made scientific sense to one of ordinary skill in the art, even if hindsight were inappropriately applied. The combined teachings of Hyder, Vagner, and Stein

would, at most, have suggested assessing whether the estrogen response elements identified by Hyder contain IRES elements in the 5' UTR alone or provide IRES induced activity under normoxic or hypoxic conditions using a bicistronic reporter gene construct described in Stein, or assessing the effect of the estrogen response elements on inducing IRES activity under normoxic and hypoxic conditions. As such, Stein does not cure the deficiencies of either Hyder, Vagner or Levy.

In view of the foregoing, Applicants submit that Hyder in view of Vagner, Levy and Stein fails to render obvious claim 48, and respectfully request that this rejection be withdrawn.

5. The Rejection over Hyder in view of Vagner, Levy, and Claffey

Claims 58 and 59 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hyder in view of Vagner and Levy and further in view of Claffey *et al.*, 1998, Mol. Cell. Biol. 9(2): 469-481 ("Claffey"). Without acquiescing to the propriety of the rejection and in order to expedite prosecution of the application, Applicants have canceled claims 58 and 59, without prejudice. Accordingly, the rejection of claims 58 and 59 is moot and should be withdrawn.

6. The Rejection over Hyder in view of Vagner, Levy, and Cho

Claims 62-65 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hyder in view of Vagner and Levy and further in view of Cho *et al.*, 2002, Expert Opin Ther Targets, 6(6): 679-689 ("Cho"). Applicants respectfully disagree with the rejection for the reasons detailed below.

As discussed above, independent claims 44 and 45, from which claims 62-65 depend, are patentable over Hyder, Vagner, and Levy because neither Hyder, nor Vagner, nor Levy teach or suggest, or provide any reason that would have prompted a person of ordinary skill in the relevant art to perform a screening assay for identifying compounds that modulate human VEGF mRNA translation governed by the untranslated regions of human VEGF mRNA by performing reporter assays using reporter constructs that encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, as required by claim 45.

Cho does not cure the deficiencies of Hyder, Vagner, or Levy. Cho is a review article that discusses techniques for the identification of novel therapeutic targets for skeletal diseases (see Cho at abstract). Nowhere does Cho teach or suggest a screening assay for identifying compounds that modulate human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA, by performing reporter assays using reporter constructs that encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, as required by claims 45 and 46. There is no teaching in Cho of VEGF, much less a teaching of a screening assay for identifying compounds that modulate human VEGF mRNA translation governed by the untranslated regions of the human VEGF mRNA.

In view of the foregoing, Applicants submit that Hyder in view of Vagner, Levy, and Cho fails to render obvious claims 62 to 65, and respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all the requirements for patentability. Consideration and entry of the foregoing amendments and remarks into the file of the application is respectfully requested. Withdrawal of all rejections and consideration of the amended claims are requested.

If any issues remain, the Examiner is urged to telephone the undersigned.

Respectfully submitted,

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